European Regulatory Framework for the Development of Cell-Based Medicines

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Chapter Outline

Guide to Cell Therapy GxP. http://dx.doi.org/10.1016/B978-0-12-803115-5.00002-4

1. Introduction

For any cell biologist specialized in translational research on a particular cell-based therapy, achievement of positive endpoint results in a proof-of-concept animal model may be one of the most exciting moments in his/her lifetime, due to the potential harnessing of application to human beings after a long and sometimes tortuous R&D program. However, that same moment could also mark the commencement of one of the most challenging and sometimes frustrating periods of their professional careers, if they decide to go a step further translating those findings into the clinical setting.

The main reason for this apparent contradiction is the complexity of the legal framework regulating cell-based products, which are technically complex per se. Most cell-based products are considered as medicines in Europe, representing a novel class named advanced therapy medicinal products (ATMPs) that comprise the following categories:

- Somatic cell therapy medicinal products (SCTMPs)
- Gene therapy medicinal products (GTMPs)
- Tissue engineered products (TEPs)
- Combined advanced therapy medicinal products

2. What Cell-Based Products are Considered as Medicinal Products? The Legal Definitions and Main Regulations Applying to Cell-Based Products

The current legal definitions of cell and GTMPs are found in Directive 2001/83/EC [1] as amended by Commission Directive 2009/120/EC [2], and the definitions of TEPs and combined ATMPs in Regulation (EC) No 1394/2007 [3] (Figure 1).

2.1 Gene Therapy Medicinal Products (GTMPs)

Although not all GTMPs involve cells, in the case of ex vivo gene therapy, cells play an essential role. Usually, we identify the concept of gene therapy simply as the insertion, alteration, or removal of genes within individual cells and biological tissues to treat a disease. Nevertheless, in gene therapy, frequently, but not necessarily

Figure 1 Regulations that define the different ATMPs in Europe.

always, a recombinant vector, which can be viral or nonviral, with the therapeutic gene is used for gene delivery to specified cells and tissues. Two different strategies are used for this gene delivery, that is, ex vivo and in vivo. In the ex vivo approach, the cells may be cultured and used for gene transfer, so that these transduced cells are then introduced in a target tissue. Alternatively, in the in vivo approach, the gene may be delivered through a vector directly into the target cell or tissue.

The most common form of gene therapy involves the insertion of functional genes into an unspecified genomic location to replace a mutated gene, but other forms involve directly correcting the mutation or modifying normal genes, for example, to make a patient resistant to a viral infection or to increase the production of a functional protein.

From the regulatory point of view, the definition of a GTMP is more precise regarding the objectives and effects, and it excludes vaccines from its scope. The definition is found in the Commission Directive 2009/120/EC [2]:

"Gene therapy medicinal product means a biological medicinal product which has the following characteristics:

1. It contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding, or deleting a genetic sequence.
2. Its therapeutic, prophylactic, or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Gene therapy medicinal products shall not include vaccines against infectious diseases."

2.2 Somatic Cell Therapy Medicinal Products (SCTMPs)

One of the simplest ways to define cell therapy can be the use of cells to treat a disease. This includes any type of cell, irrespective of its source (human-autologous or allogeneic and animal), the degree of differentiation (committed cells, progenitors, or stem cells), or their origin (embryo, fetus, newborn, or adult individuals).

A further issue concerns the concept of somatic cell therapy products within the scope of medicinal products. This definition is also found in the Commission Directive 2009/120/EC [2]:

"Somatic cell therapy medicinal product means a biological medicinal product which has the following characteristics:

1. Contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions, or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor.
2. It is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing, or diagnosing a disease through the pharmacological, immunological, or metabolic action of its cells or tissues."

For the purposes of point (1), the manipulations listed in Box 1—as detailed in Annex I to Regulation (EC) No 1394/2007 [3]—shall not be considered as substantial manipulations.

Box 1 Nonsubstantial Manipulations

- Cutting
- Grinding
- Shaping
- Centrifugation
- Soaking in antibiotic or antimicrobial solutions
- Sterilization
- Irradiation
- Cell separation, concentration, or purification,
- Filtering
- Lyophilization
- Freezing
- Cryopreservation
- Vitrification

2.3 Tissue Engineered Products (TEPs)

The first idea that springs to mind when we are speaking about TEPs is a scaffold, more or less complex, biological or not, in combination with cells. Although this may indeed be typical of a tissue engineered product, a scaffold does not necessarily need to be present for a product to be included in this category of ATMPs.
The definition is set out in the Regulation (EC) No 1394/2007 [3] as follows:

"Tissue engineered product means a product that:

- contains or consists of engineered cells or tissues, and
- is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing, or replacing a human tissue.

A tissue engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or nonviable. It may also contain additional substances, such as cellular products, bio-molecules, biomaterials, chemical substances, scaffolds, or matrices.

Products containing or consisting exclusively of nonviable human or animal cells and/or tissues, which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological, or metabolic action, shall be excluded from this definition."

Therefore, the presence of a matrix or scaffold is not necessary for a product to be considered a tissue engineered product. The key is the presence of engineered cells or tissues and the objective of its administration. When considering the concept of engineered cells or tissues, the Regulation states that

"Cells or tissues shall be considered 'engineered' if they fulfill at least one of the following conditions:

- The cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions, or structural properties relevant for the intended regeneration, repair, or replacement are achieved.
- The cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor."

If we review the aforementioned definition of SCTMPs, we will see that the composition of both SCTMPs and TEPs may be identical. Consequently, the difference rests in the second condition related to the objective of its administration. Their mode of action is different: whereas TEPs are administered with a view to regenerating, repairing, or replacing a human tissue, in the case of SCTMPs, they are administered with a view to treating, preventing, or diagnosing a disease through the pharmacological, immunological, or metabolic action of its cells or tissues.

One example of a product that can be considered as SCTMP or TEP could be substantially manipulated mesenchymal stem cells. When they are used for immunomodulation to treat an autoimmune disease, they might be classified as SCTMP; whereas, they might be classified as TEP when used to repair a bone fracture.

Hence, a TEP might be simply defined as a product containing cells or tissues that have been engineered so that they can be used to repair, regenerate, or replace tissue.

2.4 Combined Advanced Therapy Medicinal Products

The last category of ATMPs comprises the combined ATMP. Regulation (EC) No 1394/2007 [3] defines a combined ATMP as that which

"fulfills the following conditions:

- It must incorporate, as an integral part of the product, one or more medical devices or one or more active implantable medical devices, and
- Its cellular or tissue part must contain viable cells or tissues, or
- Its cellular or tissue part containing nonviable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to."

As in the previous cases, the Regulation also considers that

"where a product contains viable cells or tissues, the pharmacological, immunological, or metabolic action of those cells or tissues shall be considered as the principal mode of action of the product."

2.5 Limits between ATMPs Categories

Taking these possibilities into account, some products could fall into different categories of ATMPs, but the Regulation (EC) No 1394/2007 [3] clarifies this:

"A product which may fall within the definition of a somatic cell therapy medicinal product or a tissue engineered product, and a gene therapy medicinal product, shall be considered as a gene therapy medicinal product."

And in cases in which the difference between an SCTMP and a TEP is not clear, the Regulation establishes that

"A product which may fall within the definition of a tissue engineered product and within the definition of a somatic cell therapy medicinal product shall be considered as a tissue engineered product."

Regulation (EC) No 1394/2007 [3] establishes that any applicant developing a product based on genes, cells, or tissues may request a scientific recommendation

of the European Medicines Agency (EMA) to determine whether the referred product falls within the definition of an ATMP. The EMA shall deliver this recommendation after consultation with the Commission and within 60 days after receipt of the request. Those recommendations are available, after deletion of all information of commercial confidential nature, on the EMA website. The Regulation also establishes the creation of a Committee for Advanced Therapies (CAT) within the EMA. The CAT can provide advice on whether a product falls within the definition of an ATMP. To request ATMP classification, a Pre-submission request form and Briefing Information (including background information on scientific, legal, regulatory, and medical aspects) have to be completed and sent to AdvancedTherapies@ema.europa.eu.

In Figure 2, we can see a decision tree (available at the Paul-Ehrlich-Institut Website [4]) that may be helpful in order to know if a product falls within the ATMP group and to classify it according to the different categories.

2.6 Borderline Products

The legal definitions of the different types of ATMPs incorporate concepts not easy to apply in specific cases. Sometimes, it is not easy to decide what category corresponds with a specific product, and it is even more difficult to decide if a cell-based product is indeed a medicinal product or not. To provide guidance on the ATMP classification procedure as well as on the interpretation of the legal concepts, the EMA/CAT published a reflection paper on classification of ATMPs that has been updated to reflect the current thinking of the CAT on what medicines can or cannot be classified as ATMPs. The updated reflection paper was adopted by CAT in May 2015 after public consultation [5] and recognizes the difficulty as long as it discusses some borderline cases and areas where scientific knowledge is limited or evolving rapidly.

The key points regarding the limits to determine whether a cell-based product is or is not a medicinal product are based on the following:

- The type of manipulation performed on the cells (whether they have been subjected to substantial manipulation so that biological characteristics, physiological functions, or structural properties relevant for the intended clinical use have been altered)
- The intended use—for the same or different essential function or functions—in the recipient and the donor, irrespective of whether the donor and the recipient are the same person

Regarding what is considered substantial manipulation, the Regulation only provides a nonexhaustive list of the manipulations not considered as substantial (Box 1). The culturing of cells—one of the most common manipulations performed in the use of cells as a therapy—is generally considered substantial manipulation. In fact, according to the reflection paper, the CAT considers substantial manipulation cell culturing leading to expansion. Therefore, when a cell-based product is subjected to substantial manipulation, even if we are intending to use it for the same function in the recipient as in the donor, then we are dealing with a medicinal product.

Bearing in mind the conditions with which a cell product must comply to be considered as a medicinal product, we can find some examples of cell therapies

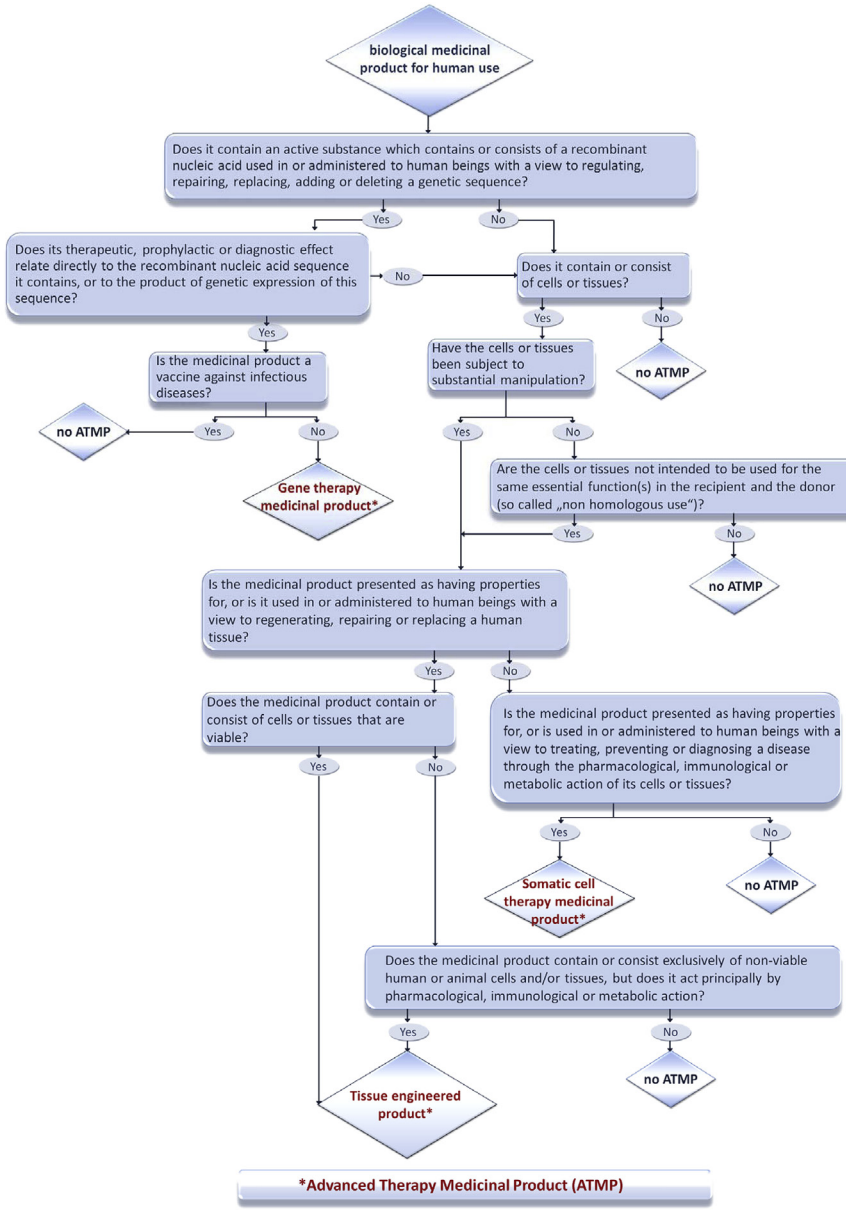

Figure 2 Decision tree for classification of medicinal products as ATMP. Paul-Ehrlich-Institut. Available in: http://www.pei.de/SharedDocs/Downloads/EN/pu/innovation-office/decision-tree-atmp.pdf?__blob=publicationFile&v=1 [accessed 06.03.15].

that are considered to be transplants rather than medicinal products. This is the case of bone marrow transplantation in which the bone marrow progenitors are nonsubstantially manipulated and the intended use is to replace the hematopoiesis in the recipient. Since among bone marrow progenitors there is a significant

number of hematopoietic progenitors, we can consider hematopoiesis to be one of the essential functions of these bone marrow progenitors in the donor. Another example of a cell therapy not considered as a medicinal product is the transplantation of pancreatic islets when these are not cultured before being transplanted. In this case, they are only purified, therefore nonsubstantially manipulated, and their intended use is the production of insulin, which represents the same essential function in the recipient as in the donor.

Nevertheless, there are other cases in which cellular products have not been substantially manipulated, and where it is not easy to determine if their function is substantial or not [6]. The concept paper reflects the interpretation made by CAT incorporating the concept of nonhomologous use of cells or tissues (not considered in the European legislation) as equivalent of their use for a different essential function leading to classifications subject of debate [7].

2.7 Main Regulations Applying to Cell-Based Products

It has been mentioned that not all cell-based products fall within the scope of the definition of SCTMPs, ex vivo GTMPs, TEPs, or combined ATMPs. Some cell-based products are considered as transfusion or transplants, and their development is regulated under a different legal framework.

Later in this chapter, the general legal framework will be explained that applies to ATMP development; therefore, here we will only underline the similarities and differences in the development of a cell-based product considered a medicinal product or not (Figure 3).

While blood cells intended for transfusion, mainly regulated through Directive 2002/98/EC [8] among others [9,10], do not share any regulation with the other two types of cell-based products, ATMP and cell transplantation share some regulation, and sometimes, the boundaries between their definitions are blurred, making classification difficult [6], as mentioned above.

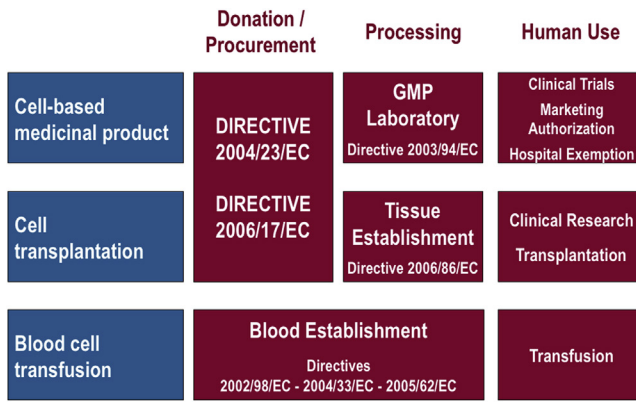

Figure 3 General legal framework for cell products.

It is important to take into account that, irrespective of whether they are considered as medicinal products or transplants, all cell-based products have to comply with the standards of quality and safety regarding donation, procurement, and testing. These standards are established in the Directive 2004/23/EC [11] on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage, and distribution of human tissues and cells and in the Commission Directive 2006/17/EC [12] implementing Directive 2004/23/EC regarding certain technical requirements for the donation, procurement, and testing of human tissues and cells.

Concerning the requirements for processing these types of products, in the case of a medicinal product, Good Manufacturing Practice (GMP) compliant facilities are required, and the principles of GMP should be followed [13]. This will be examined below at length. In the case of cell or tissue transplants, a tissue establishment is required, and it is also necessary to comply with the requirements set out in Commission Directive 2006/86/EC [14] implementing Directive 2004/23/EC [11] regarding traceability requirements, notification of serious adverse reactions and events, and certain technical requirements for the coding, processing, preservation, storage, and distribution of human tissues and cells.

Finally, the clinical use is regulated differently according to the phase of development (experimental or not) and the nature of the cell product. As we will see, in the case of medicinal products, their clinical use must follow the clinical trial regulation—when they are still considered as investigational medicinal products—or the product has to be granted marketing authorization by the EMA. There could also be another possibility for ATMPs not industrially prepared under the denominated "hospital exemption" scheme. The clinical use of cell or tissue transplants—once their safety and efficacy have been demonstrated in clinical research—is also regulated by Commission Directive 2006/86/EC [14]. The authorization pathway is completely different, not involving Medicines Agencies.

3. An Introduction to Cell-Based Medicine Development: Roadmap

Cell-based medicines are a particularly novel class of medicines and possibly constitute one of the most complex tasks that may be approached by clinical researchers when exploring new therapeutic applications. In Europe, ATMPs, including cell therapy, gene therapy, and TEPs, represent a field with a constantly evolving regulatory landscape that scientists and regulators alike find difficult to navigate. Stem cell scientists should, therefore, be aware of the intricacies of GMP implementation before initiating full-fledged translational programs, and they should also have at their disposal well-trained technologists to develop ATMPs in different laboratories and institutions—be it hospitals, academia, or industry—within Europe [15].

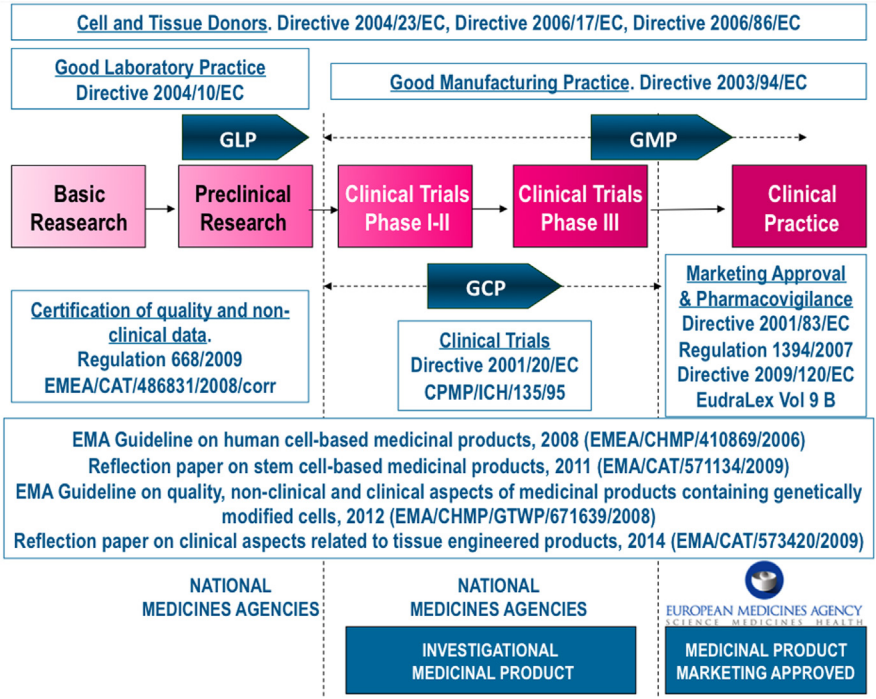

Figure 4 Relevant European rules and guidance for the ATMP development.

In as far as ATMPs are considered, a particular category of biological medicines, their development must not only fulfill the requirements for a medicinal product but also adhere to some very specific rules, and moreover, a set of EMA guidelines, concept papers, and reflection papers should be followed. Nevertheless, ATMPs are highly heterogenous, and regulatory authorities will always apply their rulings on a case-by-case basis.

Summarized in Figure 4 are the most important European rules and guidelines that must be taken into account to develop a stem cell medicinal product or other ATMPs. In the case of cell-based medicinal products, the standards of quality and safety for donation, procurement, and testing of human tissues and cell donors must also be followed.

At this point, it is important to remind the reader that this chapter will serve as an introduction for subsequent chapters that will approach specific issues in a more comprehensive manner. Therefore, the objective of this chapter is to provide a general picture to facilitate the integration of latter sections into the general roadmap for the development of ATMP. A helpful tool to identify and download the most relevant regulation and guidelines related to the ATMP development is shown in Box 2 at the end of this section.

Box 2 Additional Information on ATMP Regulation

The web page of the Andalusian Initiative for Advanced Therapies is a good resource to consult and download the main European regulations (Directives and Regulations) that regulate basic, preclinical, and clinical research with these kinds of products, their quality, and manufacturing aspects, as well as their marketing or clinic use. There is also a selection of EMA and ICH guidelines and other documents of interest related to these issues including FDA regulations and Pharmacopeias from Europe and the United States [82].

3.1 Aspects to Consider When Designing Proof-of-Concept Experiments in Animal Models

Let us imagine we have a reasonably characterized cellular product that we intend to put into human beings to treat a condition for which there is a rationale at least for a purported therapeutic effect. Human cell-based medicinal products are highly heterogenous, and regulatory authorities will always apply their rulings on a case by-case basis. When reviewing an investigational medicinal product dossier (IMPD) application, national authorities will usually require the identification of risk factors inherent in the nature of the ATMP in question and associated with its quality, safety, and efficacy [16].

As a rule of thumb, regulatory requirements will usually be less stringent for early clinical trials and will increase sharply as we approach marketing authorization. However, this is not always the case, for example, safety data for Phase I studies with stem cells may be very stringent. In any case, it may be counterproductive to rush into clinical trial testing before solid product characterization and nonclinical data are available, since, at the end of the day, the evaluation process will be further lengthened.

There are some principles that may be generally applied to all cell-based products. A good starting point for a newcomer would be the relevant chapters of the European Pharmacopoeia (Ph. Eur.) [17], EMA guidelines on cell therapy and tissue engineering [18–21], and those on gene therapy [22]. In addition, in the case of gene therapy product development, the guideline on quality, nonquality, and clinical aspects of medicinal products containing genetically modified cells should be consulted [23]. Of note, researchers in the advanced therapies area should be aware of the fast pace of regulatory changes that affect product development, with new guidelines arising every few months.

Before administration into humans, both biodistribution and toxicity of the investigational medicinal product must be tested in a relevant animal model according to Good Laboratory Practice (GLP) [24–26]. These usually involve subcontracting a contract research organization (CRO) specialized in basic pharmacology, toxicology, or safety studies so that the reports issued will comply with regulations. However,

this is not always the case: contracts with CROs may be prohibitive for many laboratories, and national regulatory agencies will sometimes accept more basic laboratory studies provided "GLP-like" conditions have been followed according to the relevant guidelines. It is, therefore, advisable to design all animal experimentation on cellular products taking into account the following relevant nonclinical study types:

- Pharmacodynamic "proof-of-concept": Homologous animal models (i.e., animal models representative of the clinical situation and thus that provide interpretable data) should be used when possible to explore the potential clinical effect of the cellular product. Usually, a disease model is looked for first, and if not available, others are tested.
- Biodistribution: Ideally, all organs must be tested after transplantation of cells (with a safety margin of 10-fold clinical dose) into animals of two different species (one rodent, one non-rodent) and of both sexes. Of note, the testing will be dependent on the product and route of administration. These animals may also be used for environmental risk assessment and gonad tests to check for unexpected germline transmission in the case of gene therapy products. In this case, follow-up must be tied to the window of detection of transgene expression.
- Dose studies: The chosen cell dose must be based on the protocol rationale, and a dose escalation study should confirm the rationale. Toxicity studies must also be taken into account when deciding dose, and a calculation of viable/effective cellular dose in the target organ must be provided. Obviously, cell dosing is not always applicable, for example, TEPs often have a defined maximum cell load, and product application does not take into account cell dose but other parameters such as construct size, surface, etc.
- Toxicity studies: They will be performed in one species (the most relevant) and with the same route and administration method as that scheduled for the clinical trial. Unless this is not possible for practical reasons, we must find a cellular dose where toxic effects are detected and explore histopathological findings, duration, and reversibility of toxicity, as well as suitable toxicity biomarkers for our product.
- Immunogenicity and immunotoxicity studies will usually be relevant when allogeneic cells are to be used and/or if multiple dosing protocol is to be performed.
- Carcinogenicity, oncogenicity, and tumorigenicity studies will seldom be necessary, although this will depend greatly on the nature of the ATMP. For instance, tumorigenicity studies are usually required if growth factors are used in cell culture/final product and/or the product contains pluripotent or multipotent stem cells.

Many of these studies can be grouped together so that relevant evidence is obtained while ensuring best possible standards in animal welfare. In addition, the EMA has published several specific guidelines on the subject of nonclinical studies of ATMPs that should be consulted at the time of protocol design. It is also good practice, and we strongly recommend, to apply for scientific advice or protocol assistance (for orphan drugs only) from the regulatory authorities, as early in the development process as possible, and as many times as necessary throughout the course of the process.

3.2 Advanced Therapies as Medicinal Products: Manufacturing Aspects

Once we have determined that a particular product falls within the ATMP category, regardless of whether it be investigational (i.e., a drug to be used in clinical trials and not yet authorized for marketing as such), production of cells, vectors, or TEPs that

will go into patients, it must comply with Good Manufacturing Practice (GMP) for medicinal products [13].

The GMP Guide is presented in two parts: basic requirements and specific annexes. GMP Part I covers all aspects in the manufacture of medicinal products, including quality assurance and risk management, and Part II deals with active substances used as starting materials [27]. In addition to Part I and II, a series of annexes providing details about specific areas of activity are included. For cell manufacturing processes, aspects of different annexes will apply (e.g., annex on sterile preparations and on biological medicinal products, among others). From a practical point of view, implementation of GMP in a cell production facility will ensure the following:

1. The existence of a quality management system
2. That there is sufficient, suitably trained personnel
3. That the premises and qualified equipment are fit for purpose and that there are separate production, quality control, and storage areas within the facilities, and cell production is being performed in a tightly controlled environment
4. That laboratory procedures are reliable and properly documented, ensuring traceability of cells and starting materials
5. That cell production operations are carried out in a controlled and reproducible (i.e., validated) manner, ensuring absence of cross-contamination
6. That the quality of cells and also the personnel, production process, and the facilities are regularly controlled
7. That the cell production facility will regularly self-inspect to monitor compliance with GMP and implement corrective measures when necessary

3.2.1 Personnel and Hygiene Needs under GMP

First and foremost, there must be sufficient qualified personnel to carry out all the tasks needed to get cells into clinical trials. All personnel should be aware of their individual responsibilities and of the GMP principles that affect them. Key posts that should be occupied by full-time personnel include the Head of Production, the Head of Quality Control, and the Qualified Person (QP) (technical director that will hold legal responsibility alongside the clinical trial Sponsor). However, this point is at the discretion of the national regulatory agencies that will often permit the doubling up of GMP responsibilities with related research, medical, or teaching duties. The heads of Production and Quality Control must be independent of each other. They should receive initial and continuing training, including hygiene instructions, as relevant to their needs. The manufacturer should provide training for all the personnel whose duties take them into production areas or into control laboratories (including the technical, maintenance, and cleaning personnel) and for other personnel whose activities could affect the quality of the product. Continuing training should also be given, and its practical effectiveness should be periodically assessed. Training records should be kept.

3.2.2 ATMP Production Facilities under GMP

Production of ATMPs will usually be performed in “cleanrooms” in which the environmental conditions (temperature and relative humidity) must be controlled, as

appropriate for the intended cell culture work. Furthermore, airborne particle concentration and sterility in the working area must be tightly controlled, so that they comply with the maximum average numbers permitted for areas within each GMP "grade" (there are four such grades, termed A–D; please refer to Chapter 5, Good Manufacturing Practice compliance in the manufacture of cell-based medicines, in this book for more details).

To further comprehend just how "clean" these average particle numbers are, it must be taken into account that the generation of contamination is proportional to operator activity. A motionless person may generate about 100,000 particles ≥ 0.5 μm per minute, and a person walking, five million particles ≥ 0.5 μm and thousands of microbe-carrying particles per minute [28]. For this reason, only the minimum personnel required should be present in clean areas, and they should restrict their movements as much as possible.

Although the layout of GMP facilities will generally depend on the nature of the ATMP to be manufactured, Figure 5 shows a representative scheme to illustrate some considerations on GMP design that are specific for cell production facilities.

As a general principle, cell production and end-product packaging must be done in separate laminar flow hoods (GMP grade A) within a grade B environment (Figure 5(A)). Both rooms will be connected through wall-mounted, pass-through chambers with an interlock system that permits transfer of materials in and out of the cleanrooms, while avoiding contamination risks. These chambers can also be equipped with UV lamps for external sterilization of materials, if needed. Manufacturing and packaging areas will usually have positive pressure to avoid entrance of contaminants from adjacent areas. However, if virus containment is needed, the cleanroom should be negatively pressurized and adjacent to a positively pressurized "barrier" entrance room. If there is more than one door in any room, a warning or locking device is fitted to avoid simultaneous opening. Entrance to the GMP area follows a series of changing rooms where garments will be changed. Annex 1 of GMP specifies clothing required for each grade. These changing rooms also serve the purpose of gradually escalating positive pressure and air quality as the operators approach and enter the cleanroom areas, to ensure that air is not transferred from an area of higher contamination to one of lower contamination (Figure 5(A)). To further avoid contamination, it is also important that operator and material inward and outward workflows cross with each other as little as possible and only in the nonclassified areas (Figure 5(B–C)).

3.2.3 ATMP Characterization

Typical regulatory concerns with cellular components are product safety, characterization of the cells, and characterization and control of their manufacturing process. With regard to safety, cell donors must be carefully screened, and the cellular product, once expanded in the production facilities through master and working cell banks, if applicable, must be checked by several standardized tests (viability, sterility, adventitious agents, genetic stability/tumorigenicity, endotoxin, *mycoplasma* infection, etc.). Cell products will usually have to be defined as for identity, purity, potency, stability, and viability. These pharmaceutical definitions are sometimes difficult to implement in the

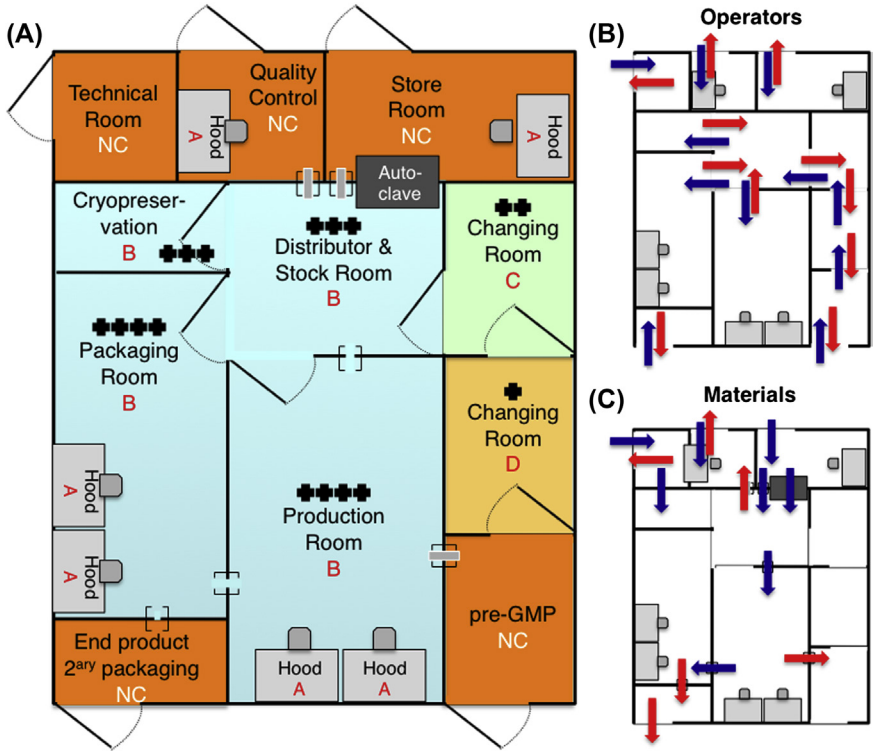

Figure 5 Technical requirements and operational workflows at an ATMP production facility under GMP. Schemes of a typical GMP facility for cell therapy and workflows of operators and materials are shown. (A) Premises will usually include nonclassified (NC, orange-colored) (dark gray in print versions) rooms as well as cleanrooms of increasing air quality (D–brown (gray in print versions), C–green (light gray in print versions), and B–blue (light gray in print versions)). Maximum air quality (A level) is usually achieved within laminar flow hoods only. Pressure (+ symbols) will increase gradually as well, to avoid contaminants entering the cleanrooms alongside the operators. GMP rules also demand that separate storage, quality control, and end-product secondary packaging areas do exist. Stock of working aliquots may be stored in clean areas. To avoid contaminants, CO_2 and liquid N_2 containers are usually left out of the cleanrooms, in a purpose-built technical room. (B) Operational workflows for personnel. Entry of personnel into the cleanrooms follows a gradient of garment changes, increasing air purity, and positive pressure. Both when entering and leaving the rooms, the operators should carry no material with them unless necessary. (C) Material flow (entry of production and exit of waste material). Materials will get into cleanrooms through autoclave, pass-through chambers, or pipes (for CO_2 and liquid N_2), and waste materials, and end product will leave them through separate pass-through chambers. Of note, operator and material workflows must cross as little as possible to avoid contamination and mistakes.

context of live cells, and they will be highly specific for the particular cell type chosen and the intended mechanism of action proposed as the rationale for the clinical trial. The manufacturing process will have to be demonstrated as aseptic (use of antibiotics is not recommended and a “media fill” validation of operational procedures must be

done in advance of protocol approval) and reproducible, lot to lot consistency being of utmost importance.

As years go by, more and more protocols for manufacturing of ATMPs under GMP have been published. These should certainly be consulted since many of the requirements that agencies will ask us to comply with are already discussed in some of these publications. Suitable manufacturing solutions for our product might already be there. A small, not comprehensive sample of relevant publications for each ATMP category follows.

1. Cell therapy
   a. Facility set up [29].
   b. Isolation and expansion of hESCs [30], mesenchymal stromal cells [31–36], and cord blood cells [37].
   c. Cell encapsulation [38,39].
   d. Process scale up [40–43].
   e. Preclinical and clinical experience with mesenchymal stromal cells [44–46].
   f. Quality risk management approach [47].
   g. Information management [48].
   h. End-product shipment [49].
   i. Cell characterization assays [50].
   j. Current status of clinical trials in the field [51,52].
2. Gene therapy
   a. Facility set up [53,54].
   b. Production of plasmid DNA as a pharmaceutical [55].
   c. Production of viruses [56].
   d. Purification and characterization of adenoviral vectors [57].
   e. Purification and characterization of lentiviral vectors [58,59].
   f. Purification and characterization of retroviral vectors [60–62].
   g. Purification and characterization of AAV vectors [63–65].
   h. Nonviral vectors for gene therapy [66].
   i. Risk assessment and biosafety considerations [67,68].
   j. Current status of clinical trials in the field [69].
   k. Regulatory aspects [70].
3. Tissue engineering
   a. Bioreactor-based engineering of cartilage grafts [71].
   b. Quality and sterility analysis of cartilage transplants [72].
   c. Translating TEPs into the clinic [73].

3.3 Clinical Research with ATMPs

Before embarking on clinical trials, researchers must have approval from an Ethical Committee or Institutional Review Board (IRB) for all centers involved as well as an authorization from the national regulatory agencies of the countries where patients will be treated. To guarantee respect of human rights, to ensure data quality, and to steer clear of avoidable errors, European Directives on Good Clinical Practice (GCP) and associated guidelines must be complied with [74–86]. Likewise, and specifically for the clinical translation of stem cells, the EMA and ISSCR guidelines [77] make a good starting point. Setting up a clinical trial may be a medium- to long-term objective for many researchers in the advanced therapies field. However, it is important to

keep in mind the significant amount of documentation that will be requested from the sponsor by regulatory authorities. Among other standardized forms, they will need to produce the following:

- Clinical trial protocol
- Investigator's brochure, that is, a compilation of clinical (if available) and nonclinical data on the investigational medicinal product(s) used in the clinical trial
- IMPD (termed investigational new drug—IND in the United States) that represents the main basis for approval to conduct clinical trials in Europe

The IMPD provides information on the quality, manufacture and control, nonclinical (toxicology and pharmacological tests) and clinical characteristics of the investigational medicinal product to be used in the clinical trial, including reference products and placebos. An overall risk–benefit assessment, critically analyzing the quality, nonclinical, and clinical data in relation to the potential risks and benefits of the proposed trial must also be included in the IMPD. Once the clinical trial is authorized and patient recruitment has started, the sponsor has a legal requirement to communicate to the regulatory authorities any adverse reactions. The sponsor's duties also include ensuring that there is an insurance policy in place to cover any liability, that recruitment of subjects is done after appropriate informed consent, and that approval of medicinal product batches for release conforms to specifications.

3.4 End of the Road: Marketing Authorization, Distribution, and Pharmacovigilance of ATMPs

If the regulatory bodies are satisfied that the quality, safety, and efficacy of an ATMP are sufficiently proven through successful clinical phases, a product can be granted a marketing authorization. This must be done through the centralized procedure at EMA [3], and approval would mean Europe-wide commercialization rights. For this reason, the requirements set are usually higher than those pertinent to clinical trial applications, since the number of patients to be potentially treated might be enormous for some prevalent conditions. The requisites and procedure for commercialization of ATMPs are outside the scope of this review since they will normally be relevant for pharmaceutical companies only. So far, there are five ATMPs that have successfully passed through marketing authorization at the EMA [78]:

1. An industrial TEP based on autologous chondrocytes expanded for cartilage regeneration (*ChondroCelect*)
2. Another TEP, also based on autologous chondrocytes but incorporated into a matrix (*MACI*; at present, its marketing authorization has been suspended for commercial reasons)
3. A GTMP containing the human lipoprotein lipase gene in an adeno-associated virus for the treatment of lipoprotein lipase deficiency (*Glybera*)
4. An SCTMP based on activated autologous peripheral-blood mononuclear cells for treatment of metastatic prostate cancer (*Provenge*)
5. A TEP consisting of ex vivo expanded autologous human corneal epithelial cells containing limbal stem cell for the treatment of limbal stem cell deficiency due to ocular burns (*Holoclar*). This product was the last one to receive a marketing authorization in February 2015.

Of note, all EU Member States permit exceptions to this authorization rule depending on the nature of the product, industrially prepared or otherwise. This is based on the exclusion considered by European Regulation for ATMPs [3] "which are prepared on a nonroutine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient." This exclusion is commonly named "hospital exemption," and it will be further explained later in this chapter.

In order to give small and medium-sized enterprises (SMEs) an incentive to conduct quality and nonclinical studies on ATMPs, a Regulation [79] came into force in 2009. Accordingly, the EMA Committee for Advanced Therapies (CAT) published a related guideline on the minimum quality and nonclinical data required for certification of ATMPs [80].

Finally, the safety of IMPs and pharmacovigilance is a key aspect of all research with ATMPs. These products are considered relatively high risk and regulatory authorities will require tight safety follow-up of ATMP-treated patients, both in clinical trials and after marketing authorization [1,16]. Once in the market, products should be consistently stored and handled as required by the marketing authorization or product specification, in accordance to Good Distribution Practice (GDP) [81], thereby maintaining the quality of the medicinal products being distributed.

4. Regional and National Institutions Supporting Cell Therapy Translational Research

Due to the innovative and complex nature and the technical specificity of cell-based medicinal products as well as the regulatory requirements for the development of translational research in this field, they are at times overwhelming for researchers and clinicians, and what is worse, they are often not successfully translated from the laboratory bench to the clinic.

Trying to fill that gap some not-for-profit organizations are promoted by regional or national governments that specifically promote the field of advanced therapies. One of the pioneering examples is the California Institute for Regenerative Medicine (CIRM [83]), which originated in 2004 when voters approved the California Stem Cell Research and Cures Initiative. CIRM was then created to fund stem cell research in the state. CIRM has quickly become a success story with an impressive list of active disease-specific projects that are reaching the clinical stage.

The Regional Government of Andalusia—having pioneered in 2003 embryonic stem cell legislation in Spain—created the Andalusian Initiative for Advanced Therapies in 2008 (IATA from the Spanish Iniciativa Andaluza en Terapias Avanzadas [84]), a publicly funded organization that gives support and training targeting researchers and clinicians needs. IATA is part of the Andalusian Public Healthcare System that offers complete health services to about 8.5 million people and comprises, among other infrastructures, 47 hospitals, around 1500 primary care centers, several research

centers and institutes, a genomic and bioinformatics platform, and a Biobank storing more than 800,000 samples from patients and normal controls—including hiPS and hES cell lines. This initiative is not only focused on funding infrastructures and research projects but is also providing global support to ATMP development and translation into the clinic. IATA coordinates a network of 10 GMP facilities to manufacture gene- and cell-based therapies [85], acts as sponsor of clinical trials (24 clinical trials so far [86]), and looks for opportunities for business collaboration. IATA also organizes a master program in manufacturing of ATMPs in collaboration with the University of Granada [87].

There are many other examples of supportive organizations more focused on accelerating the commercialization of cell-based products and technologies as well as on driving the growth of the industry [88]. Some of the best known are the Center for Commercialization of Regenerative Medicine (CCRM [89]), a Canadian not-for-profit organization established in 2011, and the UK Cell Therapy Catapult [90], established in 2012.

5. European Regulation for Advanced Therapy Medicinal Products Not Intended to be Placed on the Market: Hospital Exemption and Its National Interpretation

5.1 What Does Hospital Exemption Mean?

Regulation (EC) No 1394/2007 of the European Parliament and of the Council [3] lays down specific rules concerning the authorization, supervision, and pharmacovigilance of ATMPs. Among these rules, the aforementioned Regulation establishes a centralized marketing authorization procedure for these products when they are intended to be placed on the market or industrially prepared, amending Directive 2001/83/EC [2] and Regulation (EC) No 726/2004 [91].

However, the text of the Regulation includes the following consideration regarding its scope:

"This Regulation is a lex specialis, which introduces additional provisions to those laid down in Directive 2001/83/EC. The scope of this Regulation should be to regulate advanced therapy medicinal products which are intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process, in accordance with the general scope of the Community pharmaceutical legislation laid down in Title II of Directive 2001/83/EC. Advanced therapy medicinal products which are prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient, should be excluded from the scope of this Regulation whilst at the same time ensuring that relevant Community rules related to quality and safety are not undermined."

In fact, the Regulation (EC) No 1394/2007 in its article 28, point 2, incorporates an amendment to Directive 2001/83/EC of the European Parliament and of the Council of

November 6, 2001 on the community code relating to medicinal products for human use. The scope of this Directive is established in its article 2 as follows

"This Directive shall apply to medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process."

In article 3 it indicates that the Directive *shall not apply* to certain specific medicinal products. Article 28, point 2, of the Regulation 1394/2007, introduces a further amendment to the exclusions set out in article 3, adding the following:

"Any advanced therapy medicinal product, as defined in Regulation (EC) No 1394/2007, which is prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient.

Manufacturing of these products shall be authorised by the competent authority of the Member State. Member States shall ensure that national traceability and pharmacovigilance requirements as well as the specific quality standards referred to in this paragraph are equivalent to those provided for at Community level in respect of advanced therapy medicinal products for which authorisation is required pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council of March 31, 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency."

This article concerns what is commonly called "hospital exemption" and was included in the Regulation in recognition of the small scale and developmental nature of activity carried out in some hospitals, which calls for a degree of flexibility in the nature of regulatory requirements.

In summary, under article 28 [2] of the Regulation 1394/2007, there is an exemption from central authorization, and the Directive 2001/83/EC is not applicable to those ATMPs, which are as follows:

1. Prepared
   - **a.** On a nonroutine basis
   - **b.** According to specific quality standards
2. Used within the same Member State
   - **a.** In a hospital
   - **b.** Under the exclusive professional responsibility of a medical practitioner
3. In order to comply with an individual medical prescription
   - **a.** For a custom-made product
   - **b.** For an individual patient

Therefore, Directive 2001/83/EC does not apply to these products, but Member States have to ensure that the manufacture of ATMPs under hospital exemption is authorized by the competent national authority. In addition, traceability, pharmacovigilance, and specific quality standards must be equivalent to those to which ATMPs are subjected where centralized market authorization would be granted by the EMA.

The Directive does not specify what is meant by "industrial process" neither does the Regulation specify the meaning of a "custom-made product." Nevertheless, some countries have defined those terms. In the United Kingdom, the Human Tissue Authority has set definitions of the terms "custom-made" and "industrial process" [92]. Custom-made was defined as follows: "using a one off formulation or a formulation that has been tailored to the individual patient and prepared within the same hospital." "An industrial process would generally take place in an external facility and not within the same hospital." This is a very particular interpretation because the most important aspect here concerns the process (industrial or not), not the location, as the same process can take place in a facility inside or outside a hospital. For example, it may be possible to carry out the same custom-made process in a research center, a tissue bank, or even at a contract manufacturers' site. In fact, the scope of the hospital exemption considered in the Regulation 1394/2007 is irrespective of the type of manufacturer.

It is important to take into account that Regulation shall be binding in its entirety and directly applicable in all Members States, therefore its transposition into national law is not necessary. However, regulations can contain amendments of Directives that then again have to be transposed. Due to different interpretation, national transposition may result in variable or even conflicting provisions.

Article 28 [2] of the Regulation 1394/2007 is an amendment to Directive 2001/83/EC, and therefore, transposition into national law is necessary. Some European countries have already done this. The first were Finland, the United Kingdom, and Germany. Others have followed them and some others are in the process. All of them have to face some issues that arise in the interpretation of this Regulation, especially those related to the concept of nonroutine basis (e.g., small-scale production, nonroutine manufacturing procedures, and patient-specific product individually modified) and the specific quality standards (e.g., GMP and product specifications).

5.2 Nonroutine Basis

Regarding the definition of nonroutine basis, we can see different interpretations between countries since the European Commission has never specified any particular number to constitute nonroutine. Some examples are described next:

- The Medicines and Healthcare Products Regulatory Agency (MHRA), which is responsible for the regulatory arrangements under the exemption in the United Kingdom, takes the view that "it is not feasible to provide a simple numerical formula that would delineate the boundary between routine and nonroutine production" [93]. However, the agency considers that there are two main areas for consideration in determining whether preparation of a product by an operator is routine/nonroutine: whether it is the same product under consideration and the scale and frequency of the preparation of the specific product.

  "Where a number of different products are under consideration, the MHRA understands that the question of whether preparation is nonroutine should be considered separately in relation to each product prepared by that operator."

"Where a new product results from modifications to an earlier product, consideration of whether the new product is produced routinely is based on consideration of the pattern of production of that new product (and not that of the old product)."

In determining what constitutes the same product, the MHRA takes into consideration the nature of the advanced therapy medicinal product in question (product's mode of action and its intended use, as well as the manufacturing processes used to generate the final product, and any required product intermediates or product-specific starting materials, e.g., a genetically modified retrovirus used to transduce patient-specific stem cells).

"Repetition of preparation of the same product by an operator gives rise to the possibility that production of that product should be regarded as routine." The MHRA takes into account "the overall numbers of the particular product prepared by the operator, the regularity/frequency of production, and the time period over which the preparation of that product has become established."

- The case of the Netherlands is an example of a country that has chosen a very concrete way to define nonroutine basis. The competent authority is the Dutch Health Care Inspectorate. Under the hospital exemption, the infusion of one product for a maximum of five patients and fewer than 10 patients a year [94] is allowed.
- Germany, Finland, France, Spain, Portugal, and Italy have not yet established any number to define nonroutine. They consider the concept of hospital exemption more flexibly. Concretely, Germany, which has implemented the hospital exemption into the German Medicinal Products Act [95], has a legal definition for ATMPs prepared on a nonroutine basis as those "medicines:
  - which are manufactured in small quantities, and in the case of which, based on a routine manufacturing procedure, variations in the procedure which are medically justified for an individual patient are carried out, or
  - which have not yet been manufactured in sufficient quantities so that the necessary data to enable a comprehensive assessment are not yet available."

  The Website of the Paul-Ehrlich-Institut (PEI), the higher federal authority, set up a decision tree (Figure 6) available to inform the decision as to when the hospital exemption rule applies under the German Medicinal Products Act [96].

5.3 Quality Standards and Other Requirements

Most countries that have regulated this hospital exemption require GMP as the quality standard applicable under the hospital exemption scheme. Nevertheless, there are some differences between countries. For example, in the case of the United Kingdom, a QP is not required [97]. In Germany, "person identity" of the manufacturer is not necessary. In the Netherlands [94], France [98], and Spain [99], although GMP is required, there is some kind of flexibility.

The regulation establishes the same requirements in terms of pharmacovigilance and traceability for ATMPs independent of whether they are granted centralized market authorization by the EMA or in the case of application for hospital exemption.

Below, we specify some additional information about the requirements for applying for the hospital exemption in some European countries.

- Germany, through the PEI, gives specific authorization—Section 4b of the German Medicinal Products Act [95]—for specific products or indications. The authorization is granted

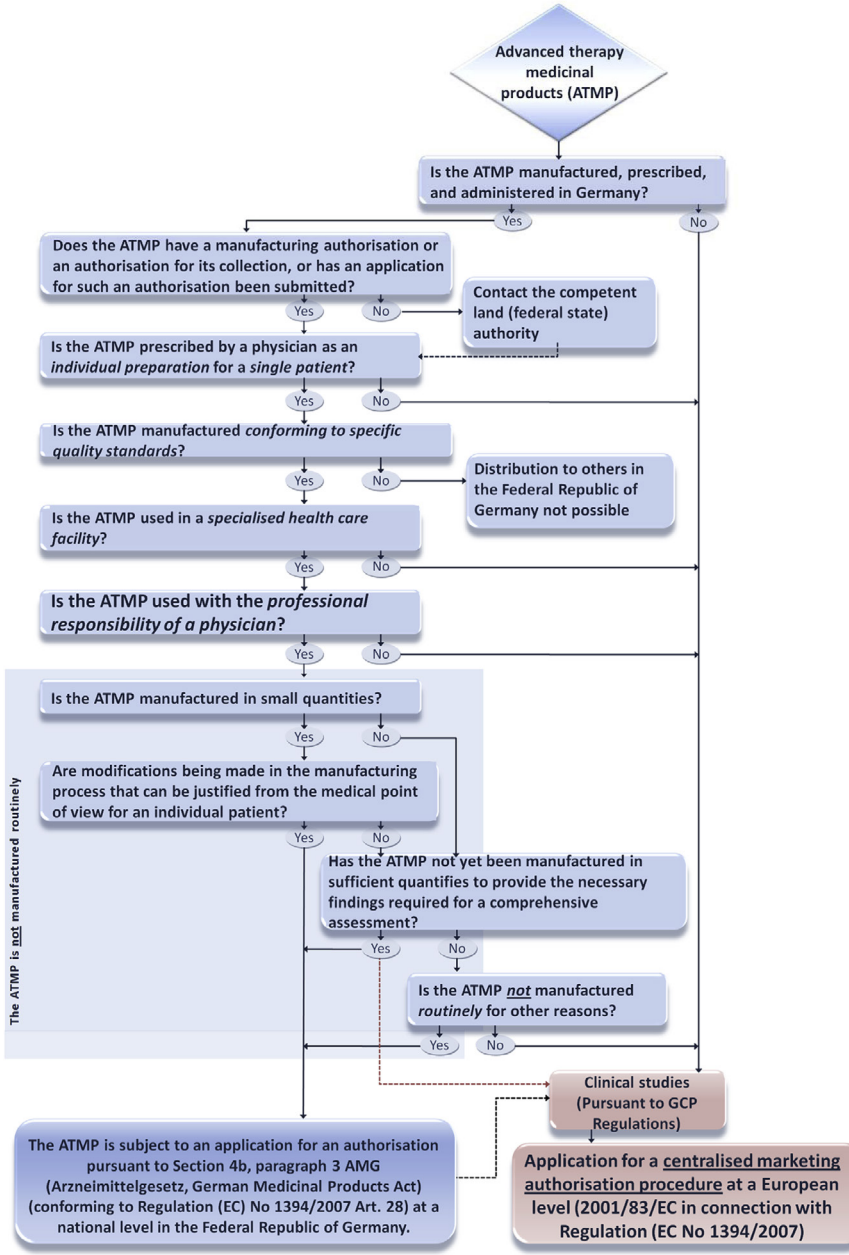

Figure 6 Decision tree for Section 4b AMG (German Medicinal Products Act). Paul-Ehrlich-Institut. Available from: http://www.pei.de/SharedDocs/Downloads/EN/pu/innovation-office/decision-tree-4b-amg.pdf?__blob=publicationFile&v=1 [accessed on 06.03.15].

not necessarily to a hospital. However, the authorized use is restricted to a specialized health care facility with proven specialization. The authorization holder has the obligation to report to the PEI the amount of preparation and knowledge required to enable the comprehensive assessment to take place. Finally, the authorization may be withdrawn or revoked by the PEI. As for every investigational medicinal product, Manufacturing Authorization is required but is issued by the competent authority of respective Laender. Therefore, in the case of hospital exemption in Germany, a manufacturing authorization is necessary as well as provisions for traceability and pharmacovigilance equivalent to those for other ATMP.

- In the case of Finland, the hospital exemption has been transposed into the Finnish legislation in the Medicines Act, Section 15c [100] (general requirements) and in the Administrative Regulation 3/2009 [101] (technical requirements). The nonindustrial manufacture of ATMPs "is subject to licence granted by the Finnish Medicines Agency (Fimea). The licence may be granted for the manufacture of a medicinal product by prescription from a physician for the individual treatment of a particular patient in a hospital. The licence may incorporate conditions pertaining to the preparation, release, traceability and use of the medicinal product or required for medicinal product safety." The application for hospital exemption manufacturing must include the following: identification of the manufacturer, description of the ATMP and product-specific quality requirements, information concerning prescribing and the doctor responsible for the patient care, description of the manufacturing process, persons responsible for the manufacturing process, manufacturing personnel; competence of the manufacturing personnel, general description concerning the quality system, manufacturing premises, critical equipment and material for the quality of the ATMP, procedure to confirm traceability requirements, procedure for serious adverse events, procedure for pharmacovigilance, declaration concerning registered personal data, and an ethical assessment and environmental effects assessment (specifically for GTMPs). Manufacturing should comply with GMP principles, and it is necessary to send an annual report to Fimea [101].
- In the United Kingdom, the MHRA has published guidance [93] that sets out the requirements relating to GMP, pharmacovigilance, traceability, and patient information under the hospital exemption. "In the UK, a manufacturer will be required to obtain a manufacturer's licence from the MHRA. The licence will authorize the manufacture of particular categories of ATMPs (gene therapy, somatic cell therapy, or tissue engineered product) rather than individual products in line with current manufacturer's licensing arrangements. ATMPs made and used under the exemption must comply with the principles of GMP." The MHRA has also included guidance on other requirements not specified in the Regulation regarding to labeling, package leaflet, advertising, and ethical issues. Manufacturers operating under the hospital exemption are required to make an annual return to the MHRA.
- In Spain [99] and Portugal [102], the licence is given to hospitals. In Spain, this licence is irrespective of the manufacturer; therefore, if several Spanish hospitals were interested in using an ATMP produced by a single manufacturer, each hospital should submit a dossier equivalent to a Common Technical Document.
- Italy [103] is about to publish a Ministerial Decree regulating the hospital exemption. The Italian Medicines Agency (AIFA, Agenzia Italiana del Farmaco) is the competent authority to authorize the manufacture of ATMPs under the hospital exemption as well as their use. The hospital exemption is only granted for public institutions, requiring authorization of the manufacturing facility, according GMP rules, and authorization of the hospital (only for public hospitals, university hospitals, or biomedical research institutes).

5.4 When to Apply for the Hospital Exemption

Perhaps the most important issue regarding hospital exemption is the situation in which the hospital exemption applies. The conditions that must be complied with are clear in the Regulation: ATMPs "prepared on a nonroutine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient" but not the circumstances in which applications should be made.

Is it possible, under this hospital exemption, to understand that it could apply before starting a clinical trial as a "proof-of-concept" in human beings? Or instead of a clinical trial? If so, should a positive decision of an ethics committee and patient insurance be in place under the hospital exemption? Is it an alternative way to compassionate use? Or, after finishing clinical trials to introduce the therapy in question as standard of care instead of a marketing approval? Or in cases where the development of products began before they were considered as medicinal products?

Some countries have attempted to answer this question, while others have not. But the answer to this question is not easy, as the Regulation does not specify that point, making different interpretations possible.

- For example, the guidance on the United Kingdom's arrangements under the hospital exemption scheme does not apply to ATMPs that will be authorized under the ATMP Regulation, for which the centralized marketing authorization procedure will apply, nor does it apply to ATMPs supplied as investigational ATMPs for use in a clinical trial.

In addition to that, the guidance incorporates a distinction between hospital exemption and specials (Table 1). "Although the two schemes are legally distinct, there are some apparent

Table 1 Summary of Some of the Main Differences in Scope between the Hospital Exemption and "Specials" Schemes in the United Kingdom

Hospital Exemption	The "Specials" Scheme
The ATMP must be prepared and used in the same EU Member State.	Products meeting the requirements of the scheme can be manufactured in the UK or imported to the UK.
The ATMP must be commissioned by a medical practitioner.	Products can be prescribed by doctors, dentists, and supplementary prescribers.
The ATMP must be custom made to meet an individual prescription and preparation must be on a "non-routine basis."	There is a special needs test (interpreted to mean the absence of a pharmaceutically equivalent and available licenced product).
The ATMP must be used in a hospital.	There is no stipulation as to location.

Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/397738/Guidance_on_the_UK_s_arrangements_under_the_hospital_exemption_scheme.pdf [accessed on 06.03.15].

similarities between the kind of activities falling within the hospital exemption and the UK "specials" scheme. Products made or supplied under either scheme are referred to as "unlicenced" since there is no product licence (marketing authorization). However, each site will need to hold a manufacturer's licence of a type specific to the scheme. It should be noted that a QP is not required for either scheme. The UK "specials" scheme, including the linked import notification scheme, permits doctors and certain other prescribers to commission an unlicenced relevant medicinal product to meet the special needs of individual patients. In principle, this latter scheme would be available for ATMPs as for any other category of medicinal product. The MHRA expects that there may in practice be a variety of situations in which small-scale production of an unlicenced ATMP is envisaged to meet requests made by a prescriber. In these circumstances operators will need to consider carefully which of the two schemes, (if either), is applicable."

In summary, the guidance specifies clearly when the hospital exemption does not apply, but it is not so clear regarding when it does. It may be possible that its purpose is to foster early stage product development.

- In Finland, the hospital exemption is understood, in some way, as a prior phase to clinical trials. Fimea has tried to tailor the quality requirements to the same level as in the first-in-man clinical trials, because then the applicants have quite easy access to the clinical trial pathway later on. The requirements are at the same level as clinical trials for quality but not for nonclinical data (not required under hospital exemption). The idea is to allow small-scale clinical use while nonclinical studies are carried out to facilitate a later clinical trial.
- In the Netherlands, the hospital exemption is applied for patients ineligible for a clinical trial (as in compassionate use) or in cases in which the product required falls outside of the specifications.
- In Italy, the hospital exemption can be granted when there is not any other alternative therapy or in case of emergency or life-threatening conditions.
- The requirements regarding quality and nonclinical information in Germany depend on the nature of the individual product, already available clinical data, and its medical need. However, at least data comparable to those of early investigational products are expected to be available. Thus, in this scenario, it might be conceivable that the hospital exemption might be applicable to facilitate or accompany a clinical trial, but also for conveying products in a preliminary "nonroutine status" on their way to centralized marketing approval.
- However, in Spain, it is only possible to apply for hospital exemption when efficacy and safety have been demonstrated, and quality, nonclinical, and clinical data must be provided. Here hospital exemption is considered as an alternative to marketing authorization for products nonindustrially manufactured and not intended to be marketed, but not as an alternative to clinical trials.

On the subject of the duration of the authorization under the hospital exemption, there is great variability between countries. At one extreme is the Netherlands, where the product-specific licence lasts for 10 batches or for one year and, at the other, Germany, where the licence is also product specific but where there is no specific period. In the case of Finland, the licence for nonindustrial manufacture of the ATMPs may be granted for a fixed or indefinite term. In Portugal, it is granted for one year, being renewable. And in Spain, authorization is initially given for three years, and for five years in successive renewals.

6. Conclusions

ATMP development is a long and risky process due to the fast pace of advancement of the science in these fields, which are currently booming. Moreover, the regulation is continuously being adapted, and thus, some degree of uncertainty will always be present while products are in the pathway to market authorization. A major conclusion of this work is that large, multidisciplinary teams with the required expertise must be assembled to be able to translate an ATMP bench to bedside.

As we have seen, hospital exemption introduced into the Regulation 1394/2007 made the Directive 2001/83 inapplicable for ATMPs "prepared on a nonroutine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient."

At the same time, the Regulation established that Member States have to ensure that the manufacture of ATMPs under the hospital exemption is authorized by the competent authority and that traceability, pharmacovigilance, and specific quality standards must be equivalent to those for ATMPs industrially manufactured.

After reviewing how this amendment of the Directive 2001/83 has been transposed into different national legislations, we can conclude that there are some important differences between countries, not only concerning the requirements to apply for the hospital exemption but also when to apply for it. Some stakeholders ask for more harmonization in the interpretation of hospital exemption within the European Union. However, hospital exemption was provided just to allow some flexibility and to enable different Member States to fit their individual circumstances to ATMP Regulation. SMEs and not-for-profit organizations (mainly universities and public hospitals) are leading the clinical development of ATMPs in Europe, with great variability among countries. In Spain and Italy, the role of industry has been minimal; while in the United Kingdom, Germany, France, Sweden, and Denmark, it has been quite important. These differences have probably been instrumental in the way national authorities have implemented hospital exemption [104].

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